HIGH THROUGHPUT MOLECULAR SCREENING ASSAY DEVELOPMENT

RELEASE DATE: January 20, 2004

RFA Number: RFA-RM-04-012

Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATION:
National Institutes of Health (NIH)
(http://www.nih.gov)

This RFA is developed as an NIH roadmap initiative (http://nihroadmap.nih.gov). All NIH Institutes and Centers participatein roadmap initiatives. The RFA will be administered by the National Institute of Neurological Disorders and Stroke (NINDS) on behalf of the NIH.

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER(S): 93.853

LETTER OF INTENT RECEIPT DATE: March 8, 2004
APPLICATION RECEIPT DATE: March 26, 2004

THIS RFA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS RFA

The purpose of this RFA is to encourage the use of high throughput molecular screening (HTS) by funding the development and adaptation of biological assays for automated screening. This is one component of the NIH Molecular Libraries and Imaging Roadmap Initiative (http://nihroadmap.nih.gov/molecularlibraries/index.asp). Other components of

the Initiative will support automated molecular screening at the Molecular Libraries Screening Centers, the creation of a chemical compound library at the Molecular Libraries Small Molecule Repository, and the development of related technologies.

RESEARCH OBJECTIVES

High throughput molecular screening (HTS) is the automated, simultaneous testing of thousands of distinct chemical compounds in models of biological mechanisms or disease. Active compounds identified through HTS can provide powerful research tools to elucidate biological processes and to do chemical genetics, or can form the basis of therapeutics development programs. The immense potential of HTS to impact the understanding of biology and disease is largely untapped because access to automated screening facilities and large compound libraries is limited in the academic community. The NIH Molecular Libraries Roadmap Initiative will provide unprecedented access to these resources and allow the broad application of HTS in NIH-supported research.

The goal of this RFA is to initiate a continuously evolving stream of scientifically and technologically outstanding assays that can be automated and used for screening at the Molecular Libraries Screening Centers. It is open to all areas of biological and biomedical research, with the goal of providing new ways to explore the functions of major components of the cell. Funding will be provided to enable investigators to transform promising assay protocols by demonstrating the responsiveness and robustness required for use in HTS. The proposed assay protocols must employ reagents and readouts that can be used in the HTS environment. Emphasis will be placed on assays that provide insight into targets, either cellular or molecular, that have not been the focus of current HTS approaches.

Many of the in vitro models of biological mechanisms and disease currently used to study the effects of specific compounds or genetic perturbations can be adapted to high throughput formats. There are a number of characteristics that make an assay suitable for high throughput approaches. The assay must be robust, reproducible and have a readout that is amenable to automated analysis. In addition, it must be possible to miniaturize the assay to a 96-well or higher density format. A broad range of models share these features, including biochemical assays, cellular models and simple model organisms such as yeast or C. elegans. This RFA will support the development of innovative assays for use in both basic research and therapeutics development programs, with an emphasis on novelty of approach to biology or disease. Appropriate assays might include but are not limited to:

o Biochemical or cell-based assays of activity or interaction involving proteins and/or other biological molecules.

o Assays of cellular or molecular phenotypes.

o Assays using model organisms such as yeast or C. elegans.

o Assays involving mutant proteins associated with disease.

o Modulation of expression of genes of interest, including effects on transcription, translation or RNA splicing.

Proposals should include assay development plans that are sufficient to demonstrate reproducibility in a low-to-moderate throughput setting, i.e., tens or hundreds of compounds, and must be feasible for adaptation to an automated, high-throughput screening approach. For example, it must be possible to reduce the assay to a 96-well or higher density format, and the assay should have a simple readout. Demonstration of feasibility for HTS must include:

o Use of reagents and readouts that can be used in an automated HTS environment.

o Demonstration of highly reproducible responses to pharmacological standards or other control conditions, including linearity of response, range of response, and acceptable signal-to-noise in a 96-well or higher density format.

o Demonstrated selectivity and reproducibility of response to a diverse collection of at least a few hundred compounds, such as a collection of FDA approved drugs or other bioactive molecules.

The applicant must provide a clear plan for evaluating the significance of the active compounds obtained in a high throughput screen using the assay. This plan should be feasible for the evaluation of a few hundred active compounds that may be identified in a primary HTS effort. The plan should include counter-screens and secondary screens to rule out artifacts and prioritize active compounds for further testing.

The overall goals for the use of the proposed assay in an HTS effort should be well defined and clearly presented. This discussion should include the expected future use of the compounds in a follow-up research program, either in the context of biological research or therapeutics development.

This RFA is intended to allow development and adaptation of screening assays for consideration for use at the NIH Molecular Libraries Screening Centers. These centers will work collaboratively with selected grantees funded under this RFA, as well as other outside investigators, to adapt assays for HTS, and will apply the assays in screening a large, diverse compound collection. Although assays developed under this RFA will be eligible for consideration by the NIH screening centers, funding under this RFA does not carry a commitment by NIH to accept the assay for screening at a center. An independent review panel will be established to select the most promising assays for testing in the HTS centers. Grantees will be free to use the assays developed under this RFA for screening elsewhere.

Adherence to the criteria described in the Research Objectives will be considered in accepting applications for review. Applications that do not meet these criteria will not be reviewed.

MECHANISM OF SUPPORT

This RFA will use the R03 Small Grant award. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. The anticipated award date is September 30, 2004. Applications that are not funded in the competition described in this RFA may be resubmitted as NEW investigator-initiated applications using the standard receipt dates for NEW applications described in the instructions to the PHS 398 application.

This RFA uses just-in-time concepts. It also uses the modular budgeting format. (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular budget format. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

FUNDS AVAILABLE

The NIH intends to commit approximately $2 million in FY 2004 to fund approximately 25 new R03 grants in response to this RFA. An applicant may request a project period of up to 1 year and a budget for direct costs of up to $50,000 per year. Although the financial plans of the NIH provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. This initiative may be repeated in future years depending on the success of the program and the availability of funds.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Domestic or foreign institutions/organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Dr. Jill Heemskerk, Molecular Library Assays
National Institute of Neurological Disorders and Stroke/NIH/DHHS
6001 Executive Boulevard, Room 2229 (MSC 9527)
Bethesda, MD 20892-9527 (20852 for overnight couriers)
Telephone: (301) 496-1779
FAX: (301) 402-1501
Email (preferred): assays@mail.nih.gov

o Direct your questions about peer review issues to:

Chief, Scientific Review Branch
National Institute of Neurological Disorders and Stroke/NIH/DHHS
6001 Executive Boulevard, Room 3208 (MSC 9529)
Bethesda, MD 20892-9529 (20852 for overnight couriers)
Telephone: (301) 496-9223
FAX: (301) 402-0182
Email (preferred): assayreview@mail.nih.gov

o Direct your questions about financial or grants management matters to:

Karen Dunlap
Grants Management Branch
National Institute of Neurological Disorders and Stroke/NIH/DHHS
6001 Executive Boulevard, Room 3248 (MSC 9537)
Bethesda, MD 20892-9537 (20852 for overnight couriers)
Telephone: (301) 496-7359
FAX: (301) 402-0219
Email (preferred): assaysgmb@mail.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

o Descriptive title of the proposed research
o Name, address, and telephone number of the Principal Investigator
o Names of other key personnel
o Participating institutions
o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

Program Director, Molecular Library Assays
National Institute of Neurological Disorders and Stroke/NIH/DHHS
6001 Executive Boulevard, Room 2136 (MSC 9527)
Bethesda, MD 20892-9527 (20852 for overnight couriers)
Telephone: (301) 496-1779
FAX: (301) 402-1501
Email (preferred): assays@mail.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SUPPLEMENTARY INSTRUCTIONS: Use the PHS 398 form with the following modifications:

o Follow instructions for preparing an R03 application at http://grants.nih.gov/grants/guide/pa-files/PA-03-108.html.

o Research Plan: Items a - d of the Research Plan (Specific Aims, Background and Significance, Preliminary Studies, and Research Design and Methods) may not exceed a total of 10 pages.

o Appendix. The appendix may include original, glossy photographs or color images of data provided that a photocopy (may be reduced in size) is also included within the page limits of the research plan. Publications or other printed material should not be included in the appendix.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS: Applications requesting up to $250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev.5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/labels.pdf.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

Center For Scientific Review
National Institutes Of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application and all copies of the appendix material must be sent to:

Program Director, Molecular Library Assays
National Institute of Neurological Disorders and Stroke/NIH/DHHS
6001 Executive Boulevard, Room 2136 (MSC 9527)
Bethesda, MD 20892-9527 (20852 for overnight couriers)

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfounded version of the application.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the Molecular Libraries Roadmap program staff. Incomplete and/or nonresponsive applications will not be reviewed.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
o Receive a written critique
o Receive a second level review by an appropriate National Advisory Council or Board.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

o Significance
o Approach
o Innovation
o Investigator
o Environment

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

FEASIBILITY FOR HTS: Although high throughput screening is outside the immediate scope of this announcement, is it feasible to adapt the proposed assay to a high throughput format? Is it likely that the assay will produce reliable results in a high throughput screen?

FUTURE PLANS: Is there an adequate plan for evaluating the activities of the compounds identified in a high throughput screen, e.g., in secondary screens? Are there important and well-defined goals for the use of active compounds identified using the proposed assay, either for use as research tools or for therapeutics development?

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific

goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL REVIEW CONSIDERATIONS

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: March 8, 2004
Application Receipt Date: March 26, 2004
Peer Review Date: July 2003
Council Review: September 2004
Earliest Anticipated Start Date: September 30, 2004

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit (as determined by peer review)
o Availability of funds
o Programmatic priorities.

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov). It is the responsibility of the applicant to

provide, in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT:
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION:
The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy

Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.healthypeople.gov/.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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Department of Health
and Human Services

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